EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Group Art Unit 1611

In re Patent Application of

Simon Michael West et al.

Serial No. 10/498,684

Confirmation No.: 9970

Filed: June 12, 2004

Examiner: Rachael E. Walter

"TRANSDERMAL TRANSPORT OF COMPOUNDS"

Electronically filed with the United States Patent and Trademark Office by Sally Sorensen on April 2, 2009.

AMENDMENT AND RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This response is timely filed April 2, 2009 in response to the non-final Office action mailed October 2, 2008. A petition for a three-month extension of time is being filed herewith. Applicants respectfully request reconsideration on the merits of the application and allowance of the claims in view of the following amendments and remarks.

Please charge any required fees or credit any overpayment to Deposit Account No. 13-3080.

Amendments to the Specification

1. Please amend the specification at paragraphs [0034]-[0037] as shown:

[0034] Preferably, the complexing agents are selected from arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:

$$NR^1R^2R^3$$

[0035] wherein R^1 is chosen from the group consisting of ~~comprising~~ straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof[[;]] and

[0036] wherein R^2 and R^3 are chosen independently from the group consisting of -H, $-CH_2(CO)OX$, $-CH_2CH(OH)CH_2SO_3X$, $-CH_2CH(OH)CH_2OPO_3X_2$, $-CH_2CH_2(CO)OX$, ~~CH_2COOX~~, $-CH_2CH_2CH(OH)CH_2SO_3X$ and $-CH_2CH_2CH(OH)CH_2OPO_3X_2$ wherein ~~and~~ X is H, Na, K or alkanolamine provided R^2 and R^3 are not both H; or ~~and~~

[0037] wherein when R^1 is $R^1(CO)$, wherein R^1 is chosen from the group consisting of straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof, and ~~then~~ R^2 is ~~may be~~ $-CH_3$ and R^3 is ~~may be~~ $-(CH_2CH_2)N(CH_2CH_{2[[4]]}(OH))[[—]]CH_2[[CHO]]PO_3H$ or R^2 and R^3 are independently ~~together may be~~ $-[[N]](CH_2)_2N(CH_2CH_{2[[4]]}(OH))CH_2(CO)OX[[—]]$, wherein X is H, Na, K or alkanolamine.

2. Please amend the specification at paragraphs [0044]-[0047] as shown:

[0044] A preferred carrier for a topical formulation according to the invention comprises a complex of tocopheryl phosphates and complexing agents are selected from arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:

$$NR^1R^2R^3$$

[0045] wherein R^1 is chosen from the group consisting of ~~comprising~~ straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof[[;]] and

[0046] wherein R^2 and R^3 are chosen independently from the group consisting of -H, -$CH_2(CO)OX$, -$CH_2CH(OH)CH_2SO_3X$, -$CH_2CH(OH)CH_2OPO_3X_2$, -$CH_2CH_2(CO)OX$, ~~CH_2COOX~~, -$CH_2CH_2CH(OH)CH_2SO_3X$ and -$CH_2CH_2CH(OH)CH_2OPO_3X_2$ wherein ~~and~~ X is H, Na, K or alkanolamine provided R^2 and R^3 are not both H; or ~~and~~

[0047] wherein when R^1 is $R^1(CO)$, wherein R^1 is chosen from the group consisting of straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof, and ~~then~~ R^2 is ~~may be~~ -CH_3 and R^3 is ~~may be~~ -$(CH_2CH_2)N(CH_2CH_{2[[4]]}(OH))[[—]]CH_2[[CHO]]PO_3H$ or R^2 and R^3 are independently ~~together may be~~ -$[[N]](CH_2)_2N(CH_2CH_{2[[4]]}(OH))CH_2(CO)OX[[—]]$, wherein X is H, Na, K or alkanolamine.

Amendments to the Claims

1. (Currently amended) A topical formulation comprising:

an effective skin-penetrating amount of one or more ~~phosphate derivatives of one or more~~ phosphorylated pharmaceutical hydroxy compounds selected from the group consisting of estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof;

one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants and amino acids having nitrogen functional groups and proteins rich in these amino acids; and

an acceptable carrier.

2. (Currently amended) The ~~A~~ topical formulation according to claim 1, wherein the topical formulation is a transdermal delivery system comprising one or more sustained zero order release systems ~~designed to alter absorption kinetics in favor of zero order release~~.

3. – 6. (Cancelled)

7. (Currently amended) A topical formulation according to claim 1 ~~6~~, wherein the complexing agents are selected from the group consisting of arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:

$$NR^1R^2R^3$$

wherein R^1 is chosen from the group consisting of ~~comprising~~ straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof[[;]] and wherein R^2 and R^3 are chosen independently from the group consisting of -H, $-CH_2(CO)OX$, $-CH_2CH(OH)CH_2SO_3X$, $-CH_2CH(OH)CH_2OPO_3X_2$, $-CH_2CH_2(CO)OX$, ~~CH_2COOX~~, $-CH_2CH_2CH(OH)CH_2SO_3X$ and $-CH_2CH_2CH(OH)CH_2OPO_3X_2$ wherein ~~and~~ X is H, Na, K or alkanolamine provided R^2 and R^3 are not both H; or ~~and~~

wherein when R^1 is $R^1(CO)$, wherein R^1 is chosen from the group consisting of straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof, and ~~then~~ R^2 is ~~may be~~ $-CH_3$ and R^3 is ~~may be~~ $-(CH_2CH_2)N(CH_2CH_{2[[4]]}(OH))[[—]]CH_2[[CHO]]PO_3H$ or R^2 and R^3 are independently ~~together may be~~ $-[[N]](CH_2)_2N(CH_2CH_{2[[4]]}(OH))CH_2(CO)OX[[—]]$, wherein X is H, Na, K or alkanolamine.

8. (Cancelled)

9. (Currently amended) A topical formulation comprising:

an effective skin-penetrating amount of one or more phosphorylated pharmaceutical hydroxy compounds selected from the group consisting of estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof; and

an acceptable carrier ~~A topical formulation according to claim 1~~, wherein the carrier comprises a complex of tocopheryl phosphate[[s]] and a complexing agent wherein the complexing agent[[s]] is ~~that are~~ selected from the group consisting of arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:

$$NR^1R^2R^3$$

wherein R^1 is chosen from the group consisting of ~~comprising~~ straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof[[;]] and wherein R^2 and R^3 are chosen independently from the group consisting of -H, $-CH_2(CO)OX$, $-CH_2CH(OH)CH_2SO_3X$, $-CH_2CH(OH)CH_2OPO_3X_2$, $-CH_2CH_2(CO)OX$, ~~CH_2COOX~~, $-CH_2CH_2CH(OH)CH_2SO_3X$ and $-CH_2CH_2CH(OH)CH_2OPO_3X_2$ wherein ~~and~~ X is H, Na, K or alkanolamine provided R^2 and R^3 are not both H; or ~~and~~

wherein when R^1 is $R^1(CO)$, wherein R^1 is chosen from the group consisting of straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof, and ~~then~~ R^2 is ~~may be~~ $-CH_3$ and R^3 is ~~may be~~ $-(CH_2CH_2)N(CH_2CH_{2[[4]]}(OH))[[—]]CH_2[[CHO]]PO_3H$ or R^2 and R^3 are independently ~~together may be~~ $-[[N]](CH_2)_2N(CH_2CH_{2[[4]]}(OH))CH_2(CO)OX[[—]]$, wherein X is H, Na, K or alkanolamine.

10. (Original) A topical formulation according to claim 9, wherein the carrier comprises lauryliminodipropionic acid tocopheryl phosphate.

11. (Original) A topical formulation according to claim 10, wherein the carrier comprises 61.95% deionized water, 5.00% glycerin, 0.05% trisodium EDTA, 0.50% carbomer, 7.50% lauryliminodipropionic acid tocopheryl phosphate, 2.00% cetearyl alcohol and ceteareth-20, 1.00% glyceryl stearate, 5.00% isopropyl myristate, 3.50% cetyl ethylhexanoate, 3.50% isocetyl behenate, 3.00% oleyl erucate, 0.50% dimethicone, 5.00% deionized water, 0.50% triethanolamine (99%) and 1.00% propylene glycol, diazolidinyl urea, methylparaben and propylparaben.

12. – 18. (Cancelled)

Remarks

No claims have been added. Claims 3-6, 8, and 12-18 are cancelled without prejudice. Claims 1, 2, 7, and 9 are amended. With entry of the amendments, claims 1, 2, 7, 9-11 will be pending. Paragraphs [0034]-[0037] and [0044]-[0047] of the specification are amended.

Claim 1 is amended to recite phosphorylated pharmaceutical hydroxy compounds selected from the group consisting of estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof. Claim 1 is also amended to recite one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants and amino acids having nitrogen functional groups and proteins rich in these amino acids. Support for the amendments to claim 1 can be found at paragraphs [0031], [0032], and [0039] of the published application. Claim 2 is amended for clarity.

Claim 7 is amended to correct typographical errors and clarify the formulas of the recited complexing agents. The errors, such as -$OPOX_2$, would have been evident to one of skill in the art at the time of the invention. Likewise the clarifications, such as C_2H_4 = CH_2CH_2, would have been evident to one of skill in the art at the time of the invention. The specification is also amended at paragraphs [0034] to [0037] to correct and clarify the same formulas.

Claim 7 is additionally amended to make claim 7 properly depend from claim 1. Claim 7 was previously dependent upon claim 6, however the subject matter of claim 6 has been incorporated into claim 1.

Claim 9 is amended to recite a topical formulation comprising an effective skin-penetrating amount of one or more phosphorylated pharmaceutical hydroxy compounds selected from the group consisting of estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof, and an acceptable carrier. Support for the amendment to claim 9 can be found at paragraphs [0024], [0031], [0032], and [0039] of the published application.

Claim 9 is additionally amended to correct typographical errors and clarify the formulas of the recited complexing agents. The errors, such as -$OPOX_2$, would have been evident to one of skill in the art at the time of the invention. Likewise the clarifications, such as C_2H_4 = CH_2CH_2, would have been evident to one of skill in the art at the time of the invention. The specification is also amended at paragraphs [0044] to [0047] to correct and clarify the same formulas.

No new matter has been entered by way of these amendments.

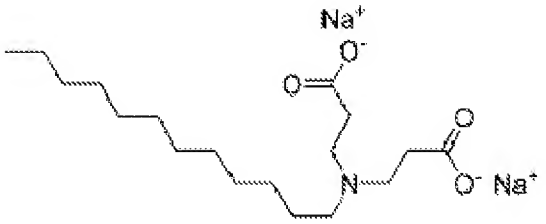
Rejections Under 35 U.S.C. § 112

Claims 1-11 are rejected under 35 U.S.C. § 112, ¶ 1 as being non-enabled. The examiner indicates, however, that the specification is enabling for estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, and morphine phosphate ester. Office action at 5. The applicants do not acquiesce to the examiner's enablement rejection, and expressly reserve the right to challenge this conclusion in a later filed continuation application. In order to facilitate and expedite an allowance, however, independent claims 1 and 9 have been amended to both recite "one or more pharmaceutical hydroxy compounds selected from the group consisting of estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof." Accordingly, withdrawal of the rejection of these independent claims, as well as their dependent claims, is respectfully requested.

Claims 2 and 6-11 are rejected under 35 U.S.C. § 112, ¶ 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Office action at 7. The examiner states that the term "in favor of" in claim 2 is a relative term which renders the claim indefinite. Claim 2 has been amended so that "zero-order" modifies "release system." Accordingly, withdrawal of the rejection is respectfully requested.

Regarding claims 6-9, the examiner states that it is unclear if the phosphate derivative of the hydroxy compound is merely associated to the complexing agent (e.g., a salt), or if there is a covalent bond formed between the reactants. Office action at 7. For examination purposes, the examiner reads compositions where a phosphate derivative of a hydroxy compound and a complexing agent are both present as a composition comprising a "complex of one or more phosphate derivatives of one or more hydroxy compounds." Id. Applicants agree with examiner's interpretation of the claims, and request withdrawal of the rejection.

The examiner additionally suggests that claim 9 does not provide sufficient antecedent basis for "lauryliminodipropionic acid" in claim 10, because lauryliminodipropionic acid is an imine complexing agent, rather than an amine complexing agent, as is recited in claim 9. Office action at 7. Applicants submit that lauryliminiodipropionic acid is, in fact, a tertiary substituted amine, the tertiary substituents being a lauryl group and two propionate groups. The use of the term "imino" is a misnomer, but prevalent in the industry. For reference, applicants submit a product sheet for Deraphat 160 (Sodium Lauriminodipropionate) from Cognis. As evidenced by the product data sheet, Sodium Lauriminodipropionate corresponds to CAS Registry No. 14960-06-6, which corresponds to the structure below:



The above structure is a species of the genus of complexing agents recited in claim 9. Accordingly. withdrawal of the rejection is respectfully requested.

Applicants respectfully submit that independent claims 1 and 9 comply with the requirements of 35 U.S.C. § 112. Claims 2 and 7, which depend from independent claim 1, and claims 10 and 11, which depend from claim 9, also meet the requirements of 35 U.S.C. § 112. Withdrawal of the 35 U.S.C. § 112 rejections of claims 1, 2, 7, 9-11 is respectfully requested.

Prior Art Rejections

Claims 1 and 3-5 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,041,434 to Lubkin ("Lubkin"). Claims 2 and 6-8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lubkin in view of U.S. Patent No. 4,686,211 to Hara et al. ("Hara"). Claims 9 and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lubkin in view of JP 11-199465 to Yashiro et al. ("Yashiro"). Claim 11 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Lubkin in view of Yashiro, and in further view of U.S. Patent Nos. 5,804,168, 5,928,631, and 6,096,326.

Independent Claim 1

As set forth above, claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Lubkin. Lubkin discloses a topical drug application for the alleviation of keratoconjunctivitis sicca (dry eye syndrome) comprising a solution of sex steroids or their derivatives suspended or dissolved in a vehicle. Abstract.

Lubkin, however, does not teach or suggest the subject matter of amended claim 1. Lubkin does not teach or suggest, among other things, a topical formulation comprising an effective skin-penetrating amount of one or more phosphorylated pharmaceutical hydroxy compounds selected from the group consisting of estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof; one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants and amino acids having nitrogen functional groups and proteins rich in these amino acids; and an acceptable carrier. Accordingly,

withdrawal of the rejection is respectfully requested. Reconsideration and allowance of claim 1 are respectfully requested.

Independent Claim 9

Claim 9 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Lubkin in view of Yashiro. Yashiro discloses skin formulations comprising tocopheryl phosphate and polyhydric alcohol. Abstract. Yashiro discloses that phosphoric acid esters of tocopheryl may be combined with thousands of other compounds to produce skin external preparations. Paragraphs [0007] – [0018]. Among the compounds recited is "—alkyl imino dipropionic acid salt." Paragraph [0015].

Applicants respectfully submit that one of skill in the art at the time of the invention would not have been motivated to combine Lubkin with Yashiro. Lubkin is directed to the preparation and application of estrogen and its derivatives in lipid or aqueous vehicles for the topical treatment of ocular surface tissues (i.e., eye drops). Lubkin, col. 1, lines 11-13. In contrast, Yashiro is directed to stable emulsification systems for delivering tocopherol (Vitamin E). Yashiro, paragraph [0003]. The stable emulsification systems of Yashiro make possible topical formulations for delivering tocopherol. Yashiro, paragraph [0005]. Lubkin, however, does not teach or suggest incorporating estrogens into skin formulations. Additionally, Yashiro does not teach or suggest incorporating estrogen or any other pharmaceutical hydroxyl compound. Because Lubkin and Yashiro are far afield, and neither suggests incorporating elements of the other reference, it is unclear why one of skill in the art at the time of the invention would have been motivated to combine Lubkin and Yashiro.

Nonetheless, assuming *arguendo* that one skilled in the art would be motivated to combine Lubkin and Yashiro, Lubkin and Yashiro, taken separately or combined, still do not teach the subject matter of independent claim 9. Nowhere in Yashiro is a carrier comprising a complex of tocopheryl phosphate, wherein the complexing agent is selected from the group recited in claim 9, suggested, let alone exemplified. Instead, lauryliminodipropionic acid is a subspecies of a compound recited in a laundry list of compounds stretching four pages. Accordingly, Yashiro gives no indication as to why a carrier comprising a complex of tocopheryl phosphate, wherein the complexing agent is selected from the group recited in claim 9, would be particularly effective in delivering phosphorylated pharmaceutical hydroxy compounds selected from the group consisting of estrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof. Yashiro merely discloses that phosphoric esters of tocopheryl may be

combined with a long list of compounds (paragraphs [0007]-[0018]) to produce external skin preparations. Because a *prima facie* case of obviousness has not been established, applicants respectfully request that the rejection of claim 9 under 35 U.S.C. § 103(a) be withdrawn.

In view of the arguments above, independent claims 1 and 9 are allowable. Reconsideration and allowance of claims 1 and 9 are respectfully requested.

Dependent Claims 2, 7, 10, 11

Claims 2 and 7 depend from allowable independent claim 1, and therefore are allowable. Claims 10 and 11 depend from allowable independent claim 9, and therefore are allowable. The claims may contain additional patentable subject matter for reasons not discussed herein.

While claim 11 is allowable, being dependent upon allowable claim 9, applicants additionally suggest that the outstanding rejection of claim 11 as unpatentable over Lubkin in view of Yashiro and in further view of U.S. Patent No. 5,804,168 to Murad ("Murad"), U.S. Patent No. 5,928,631 to Lucas et al. ("Lucas"), and U.S. Patent No. 6,096,326 Wikholm ("Wikholm") is improper.

As noted by the Supreme Court in KSR v. Teleflex, "The mere fact that references can be combined or modified does not render the resultant combination obvious." 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007). Applicants strongly disagree with the examiner's conclusions that one of skill in the art at the time of the invention would have achieved the subject matter of claim 11 in view of the five combined references. See Office action at 15-16. One of skill in the art at the time of the invention would have had little expectation of achieving a formulation capable of transdermally delivering estrogens and testosterone by merely reading the five cited references as "a list and selecting a known compound to meet known requirements." Office action at 15. While most of the cited art is concerned with skin formulations, only Lubkin is concerned with the delivery of pharmaceutical hydroxy compounds.

Because claims 2, 7, 10, 11 depend from allowable claims 1 and 9, and in view of the above arguments, reconsideration and allowance of claims 2, 7, 10, 11 are respectfully requested.

Double Patenting Rejections

Claims 1, and 3-8 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 14, 19, 23-26, 30, and 34 of U.S. Patent Application No. 10/416,774 to West et al. in view of U.S. Patent Application No. 10/5,908,846 to Bundgaard et al. Applicants respectfully request that this rejection be held in

abeyance pending the final disposition of the claims of this application or the claims of U.S. Patent Application No. 10/416,774.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. Favorable consideration of the present application as amended is therefore respectfully requested. If a conference call would be useful in resolving issues arising from the filing of this communication, please contact the undersigned at the below-noted number.

Respectfully submitted,

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